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## Case 33-2014: A 60-Year-Old Man with Bone Pain

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 Ambrose J. Huang, M.D., and Darcy A. Kerr, M.D.

### PRESENTATION OF CASE

From the Division of Hematology Oncology, Department of Medicine (E.C., E.C.A.), and the Departments of Radiation Oncology (K.S.O.), Radiology (A.J.H.), and Pathology (D.A.K.), Massachusetts General Hospital, and the Departments of Medicine (E.C., E.C.A.), Radiation Oncology (K.S.O.), Radiology (A.J.H.), and Pathology (D.A.K.), Harvard Medical School — both in Boston.

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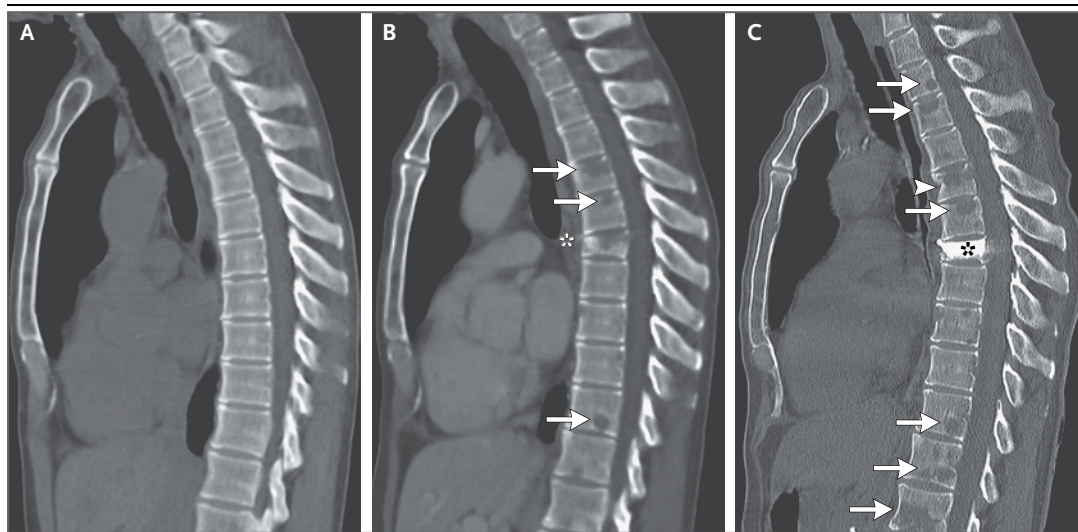
**Nurse Practitioner Mark S. Brezina (Hematology):** A 60-year-old man was seen in the outpatient cancer center at this hospital because of bone pain and skeletal lesions on imaging.

The patient had been well until approximately 2 months before this evaluation, when he had a gradual onset of pain in the back of his neck and shoulders, which was followed later by a sharp pain in the middle of his back that began suddenly after sneezing. The pain increased after exercise and did not decrease with physical therapy, massage therapy, or a course of prednisone.

**Dr. Ambrose J. Huang:** One month before this evaluation, computed tomography (CT) of the chest that was performed at another hospital revealed numerous lytic lesions in the thoracic spine and pathologic compression fractures of T5 and T7 (Fig. 1). Magnetic resonance imaging (MRI) of the lumbar spine with short-tau inversion recovery (STIR) parameters (also performed at the other hospital at that time) revealed numerous lesions with high signal intensity involving the vertebral bodies and posterior elements (Fig. 2).

**Nurse Practitioner Brezina:** Pathological examination of a bone marrow–biopsy specimen that was obtained at that time reportedly revealed mildly hypocellular bone marrow with maturing trilineage hematopoiesis. Immunoperoxidase stains for CD34, CD117, CD3, CD20, and CD138 and in situ hybridization for kappa and lambda light chains showed no abnormal cells. Examination of the bone marrow aspirate revealed maturing trilineage hematopoiesis and scattered mast cells, including occasional cells with an atypical spindle-shaped appearance. Flow cytometric and cytogenetic analysis showed a normal male karyotype; fluorescence in situ hybridization (FISH) testing for a *CHIC2* deletion associated with *FIP1L1-PDGFR*A fusion was negative. A narcotic analgesic agent was administered. The level of prostate-specific antigen (PSA) was 2.9 ng per milliliter.

One week later, a CT-guided biopsy of a lesion in the iliac crest was performed, and examination of the specimen reportedly revealed slightly hypocellular marrow and a mildly increased number of CD117+ mast cells, including spindle-shaped cells. A kyphoplasty procedure was performed at T7 for pain relief; pathological examination



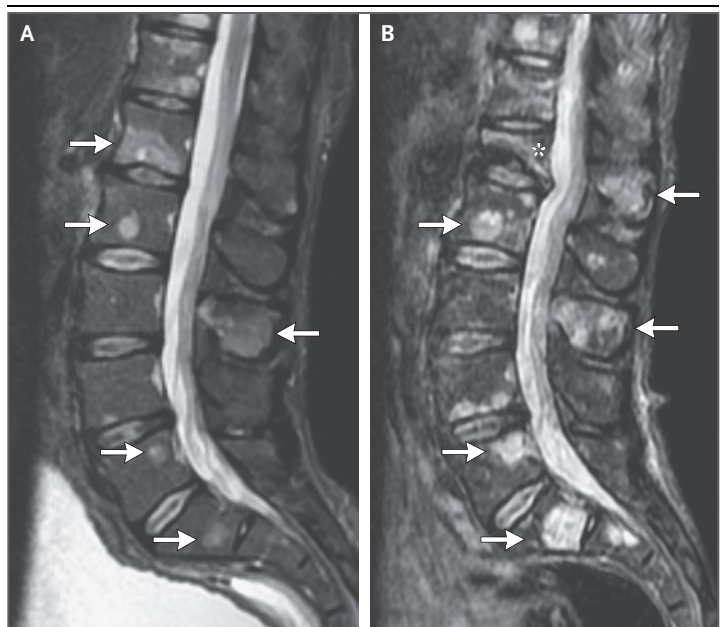
**Figure 1. CT Scans of the Thoracic Spine.**

On a sagittal reformatted image obtained 9 months before the initial presentation (Panel A), no lytic lesions are present. On an image obtained 1 month before presentation (Panel B), there are numerous lytic lesions at T5, T6, and T11 (arrows); a lytic lesion at T7 has resulted in a pathologic compression fracture and an approximately 50% loss of height (asterisk). On an image obtained 1 week before presentation (Panel C), there is an increase in the size and number of lytic lesions (arrows), progression of a previously minimal pathologic compression fracture of T5 (arrowhead), and evidence of vertebral augmentation at T7 (asterisk).

of a biopsy specimen of the T7 vertebra reportedly revealed necrosis, fibrosis, and bone remodeling, with prominent osteoclastic activity. Immunohistochemical analysis revealed a few CD117+ mast cells in fibrotic marrow, with no definite coexpression of CD2 or CD25 cells. Ghosts of spindle-shaped cells were observed in necrotic areas. The hematocrit was 37.8% (reference range, 41.0 to 53.0), the erythrocyte sedimentation rate 74 mm per hour (reference range, 0 to 15), and the blood level of tryptase 20 ng per milliliter (reference range, 2 to 10). The white-cell count and differential count were normal, as were blood levels of electrolytes and  $\beta_2$ -microglobulin, results of liver-function tests and serum protein electrophoresis, and the 24-hour urinary histamine level. Testing for antibodies to human immunodeficiency virus types 1 and 2 was reportedly negative, as was FISH analysis for the BCR-ABL rearrangement and testing of peripheral-blood leukocytes for the Janus kinase 2 (JAK2) V617F mutation and the KIT D816V mutation.

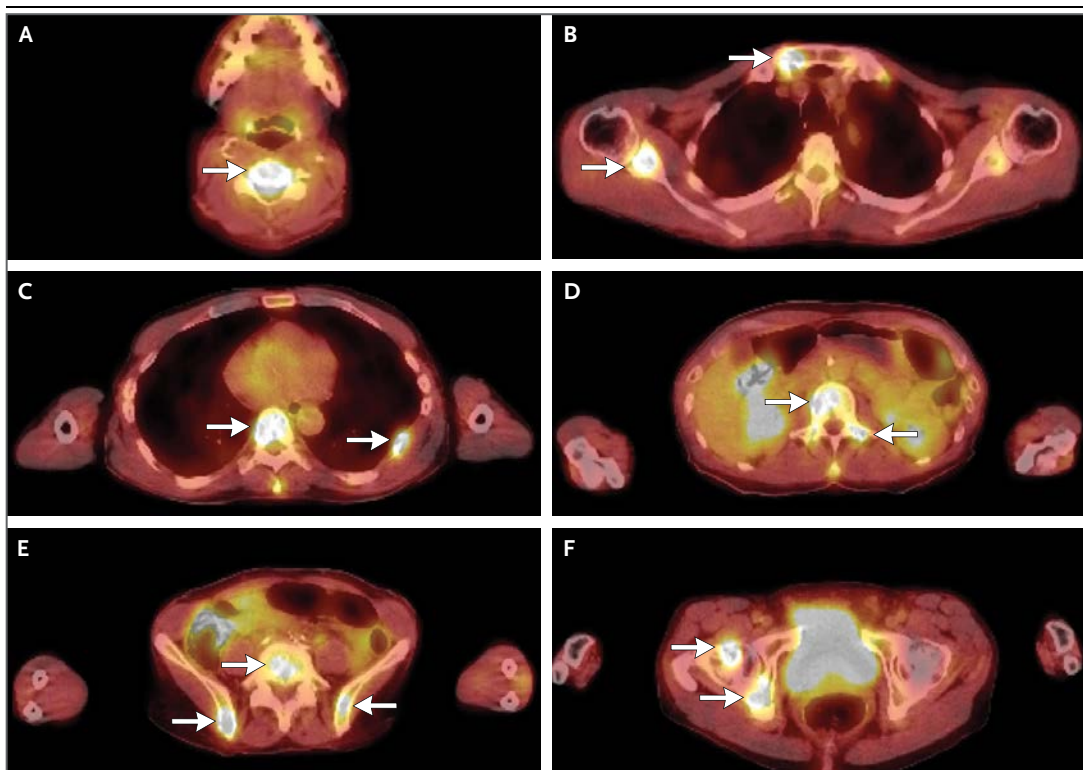
*Dr. Huang:* Nine days before the current evaluation,  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron-emission tomography and CT (PET-CT) revealed FDG-avid lesions throughout the axial and appendicular skeleton (Fig. 3).

*Nurse Practitioner Brezina:* The day before this



**Figure 2. MRI Scans of the Lumbar Spine.**

A sagittal image obtained with short-tau inversion recovery (STIR) parameters 1 month before presentation (Panel A) shows numerous lesions with high signal intensity throughout the vertebral bodies and posterior elements of the lumbar spine (arrows). An image obtained with STIR parameters 2 months after the diagnosis (Panel B) shows an increase in the size and number of lesions with high signal intensity (arrows). A lesion at L1 has resulted in a pathologic compression fracture, with approximately 50% loss of height (asterisk).



**Figure 3.** Combination  $^{18}\text{F}$ -Fluorodeoxyglucose (FDG) Positron-Emission Tomography and CT (PET-CT) Scans.

On axial PET-CT images, there are FDG-avid lesions in numerous bones, including the cervical spine (Panel A, arrow), sternum and right scapula (Panel B, arrows), thoracic spine and left eighth rib (Panel C, arrows), upper lumbar spine (Panel D, arrows), lower lumbar spine and iliac bones (Panel E, arrows), and right ischium and right femoral head (Panel F, arrows).

evaluation, the patient was seen in the allergy and immunology clinic at a second hospital. Physical examination revealed no cutaneous urticaria, urticaria pigmentosa, or angioedema. Review of the bone marrow aspirate and biopsy specimens and the iliac bone and vertebral-body biopsy specimens showed features that were interpreted as suspicious for but not diagnostic of systemic mastocytosis; repeat biopsy of a bone lesion and the administration of interferon- $\alpha$  were recommended. The next day, the patient was seen in the cancer center at this hospital.

The patient reported severe pain in the neck, back, and pelvic bone, as well as decreased appetite and a weight loss of 4.5 kg during the previous 2 months, intermittent mild heartburn, and no flushing, tachycardia, pruritus, urticaria pigmentosa, or diarrhea. Urinary retention had developed after initiation of pain medications, and he reported psychological stress and anxiety. He had a history of shingles, and until 5 years before this illness, he had had occasional episodes

of syncope when standing. There was no history of gastric ulcers, bone fractures, abnormal blood counts, allergic rhinitis, heart disease, or prior surgeries. Medications included alprazolam, mirzapine, zoledronic acid (administered once by infusion 1 week earlier), a fentanyl patch, hydromorphone, and tamsulosin (for urinary retention after the administration of pain medication). He had no known allergies. He was married and worked at a health care organization. He had a smoking history of 40 pack-years, currently smoked a half pack of cigarettes per day, and drank alcohol occasionally. His mother was over 90 years of age and had dementia, and his father had died at 84 years of age with coronary artery disease and prostate cancer; there was no family history of hematologic cancers.

On examination, the patient was alert, oriented, and in pain. The vital signs and oxygen saturation were normal. There was mild midepigastria tenderness on deep palpation, without rebound, and tenderness on palpation of the spine in the



mid-thoracic and lumbosacral regions. The remainder of the examination was normal. The hematocrit was 37.8%, the blood level of lactate dehydrogenase 251 U per liter (reference range, 110 to 210), the globulin level 4.4 g per deciliter (reference range, 2.3 to 4.1), the uric acid level 3.4 mg per deciliter (202  $\mu$ mol per liter; reference range, 3.6 to 8.5 mg per deciliter [214 to 506  $\mu$ mol per liter]), and the tryptase level 23.2 ng per milliliter (reference value, <11.5); the platelet count, red-cell indexes, and results of renal- and liver-function tests were normal, as were blood levels of electrolytes, glucose, total protein, albumin, and parathyroid hormone. Urinalysis revealed 1+ ketones and trace occult blood.

A diagnostic procedure was performed.

#### DIFFERENTIAL DIAGNOSIS

*Dr. Eyal C. Attar:* All the discussants are aware of the diagnosis in this case. The most striking clinical features of this patient's presentation were his severe bone pain and the presence of innumerable lytic bone lesions. The differential diagnosis can be generated on the basis of the radiologic findings. In general, bone lesions can be divided into two major types according to their radiologic appearance. Lytic lesions have a characteristic "moth eaten" appearance on imaging studies, which is caused by the juxtaposition of degraded bone and unaffected, calcified bone. The process of bone degradation is mediated by osteoclasts, which are activated by such molecules as interleukin-6, interleukin-3, interleukin-7, receptor activator of nuclear factor  $\kappa$ B ligand (RANKL), macrophage inflammatory protein 1 $\alpha$  (MIP-1 $\alpha$ ), and parathyroid hormone-related peptide (PTHrP). In contrast, blastic bone lesions reflect increased bone formation, a process mediated by increased osteoblastic activity. Molecules that have been implicated in this process include endothelin-1, platelet-derived growth factor (PDGF), bone morphogenic proteins, and PSA. The differential diagnosis of the various types of bone lesions is summarized in Table 1.

In this patient, the subacute presentation of bone pain in the months preceding the diagnosis rules out congenital causes, and the absence of fevers and other signs of infection makes osteomyelitis unlikely. There is no evidence of trauma or endocrinologic disorders to suggest hyperparathyroidism. Thus, primary or secondary neoplastic causes are most likely.

#### PRIMARY AND METASTATIC BONE TUMORS

Primary bone tumors, such as osteomas and osteosarcomas, have characteristic findings on radiologic examination that were not observed on imaging in this case. Furthermore, such tumors are usually manifested by one or a few bone lesions rather than by the innumerable bone lesions observed here. The presence of multiple widespread bone lesions suggests a metastatic tumor; most common are lung or prostate cancer, renal-cell carcinoma, and melanoma. Tumors that metastasize to the bone often have characteristic biologic and radiologic characteristics; prostate cancer, carcinoid tumors, small-cell lung cancer, Hodgkin's lymphoma, and medulloblastoma often cause osteoblastic lesions, whereas renal-cell carcinoma, non-small-cell lung cancer, thyroid cancer, melanoma, and lymphomas predominantly cause osteolytic lesions. Many metastatic tumors, particularly sarcomas and cancers of breast and gastrointestinal origin, may cause both lytic and blastic lesions. In general, these lesions can manifest in various ways.

In this case, the acute development of pain, coupled with multiple lytic bone lesions, suggests a malignant process. Lymphoma is unlikely on the basis of the results of the PET-CT scans, which do not indicate lymphadenopathy (although non-Hodgkin's lymphomas may originate in bone), and of the bone marrow–biopsy studies, which do not reveal abnormal lymphoid cells. Genetic studies of the bone marrow were negative for the JAK2 V617F mutation and the BCR-ABL rearrangement, findings that are associated with some myeloproliferative neoplasms. The absence of visceral masses rules out many of the solid tumors listed in the differential diagnosis. The normal levels of thyrotropin and PSA decrease the likelihood that the lytic bone lesions represent thyroid or prostate cancer.

#### MASTOCYTOSIS AND PLASMA-CELL MYELOMA

Two hematopoietic cancers that require special consideration are systemic mastocytosis and plasma-cell (multiple) myeloma. Systemic mastocytosis is associated with lytic or mixed lytic and blastic bone lesions, as well as cutaneous manifestations and allergic symptoms. Biopsy specimens of both the bone marrow and a bone lesion reportedly contained some tryptase-positive CD117+ mast cells, a finding suggestive of mastocytosis. However, in this patient, the characteristic KIT D816V mutation in peripheral-

**Table 1. Partial Differential Diagnosis of Bone Lesions.\***

Condition	Appearance of Lesion on Imaging Studies†		
	Lytic	Blastic	Mixed
Osteomyelitis (infectious)	Acute	Chronic or healed	
Hyperparathyroidism (endocrinologic)	x		Healing or regressing
Conditions that originate in bone			
Osteoma		x	
Osteoid osteoma			x
Osteosarcoma		x	x
Ewing's sarcoma	x		
Giant-cell tumor	x		
Simple bone cyst	x		
Aneurysmal bone cyst	x		Healing or regressing
Paget's disease	Acute		Chronic
Fibrous dysplasia	x		Healing or regressing
Fibroanthoma	x		Healing or regressing
Enchondroma	Possibly lytic in hands and feet		x
Lipoma	x		Ossified or partially ossified
Langerhans'-cell histiocytosis	x		Healing or regressing
Conditions that do not originate in bone			
Hematopoietic cancers			
Myeloma	x	POEMS syndrome or osteosclerotic myeloma	
Hodgkin's lymphoma		x	
Non-Hodgkin's lymphomas	x		
Mastocytosis	x	x	
Nonhematopoietic cancers			
Breast cancer	x	x	x
Lung cancer	x	x	x
Prostate cancer		x	
Melanoma	x		
Renal cancer	x		
Carcinoid tumor		x	
Gastrointestinal cancer	x	x	
Thyroid cancer	x		
Medulloblastoma		x	
Neuroblastoma	x		
Metastatic tumor of unknown primary site	x	x	x

\* Data are from Brant and Helms,<sup>1</sup> Currie et al.,<sup>2</sup> Ho and Lipper,<sup>3</sup> Manaster et al.,<sup>4</sup> and Stoller.<sup>5</sup> POEMS denotes polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes, and x indicates the presence of the condition.

† The most common appearances of lesions on imaging studies are described, but exceptions can occur with virtually any tumor. Renal-cell carcinoma is the only tumor in which blastic metastases almost never occur. The Mixed column includes lesions that have both lytic and blastic components.

blood leukocytes that is seen in 90% of patients with systemic mastocytosis was not observed,<sup>6</sup> the serum tryptase level was only minimally elevated as compared with the median level of 67 ng per milliliter that is seen in affected patients,<sup>7</sup> the characteristic rashes that are observed in patients with systemic mastocytosis (e.g., urticaria pigmentosa and telangiectasia macularis eruptiva perstans) were absent, and there were no allergic symptoms.

Plasma-cell myeloma is characterized by an increase in clonal plasma cells in the bone marrow and the presence of a monoclonal paraprotein in the serum, as well as an abnormal calcium level and hematologic, renal, and bone abnormalities, including lytic bone lesions. The absence of increased clonal plasma cells in the marrow and of a detectable paraprotein in the serum makes myeloma unlikely. A rare variant, nonsecretory myeloma, may occur, in which lytic bone lesions are present but a monoclonal paraprotein is not detected.

Examination of two prior bone marrow samples did not reveal a specific cause for this patient's painful lytic lesions. We suspected a metastatic tumor of unknown primary site, with nonsecretory myeloma and systemic mastocytosis as remote possibilities. Therefore, to acquire additional diagnostic information, four additional bone marrow biopsies and aspirations were performed.

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#### DR. EYAL C. ATTAR'S DIAGNOSIS

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Metastatic malignant tumor of unknown primary site.

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#### PATHOLOGICAL DISCUSSION

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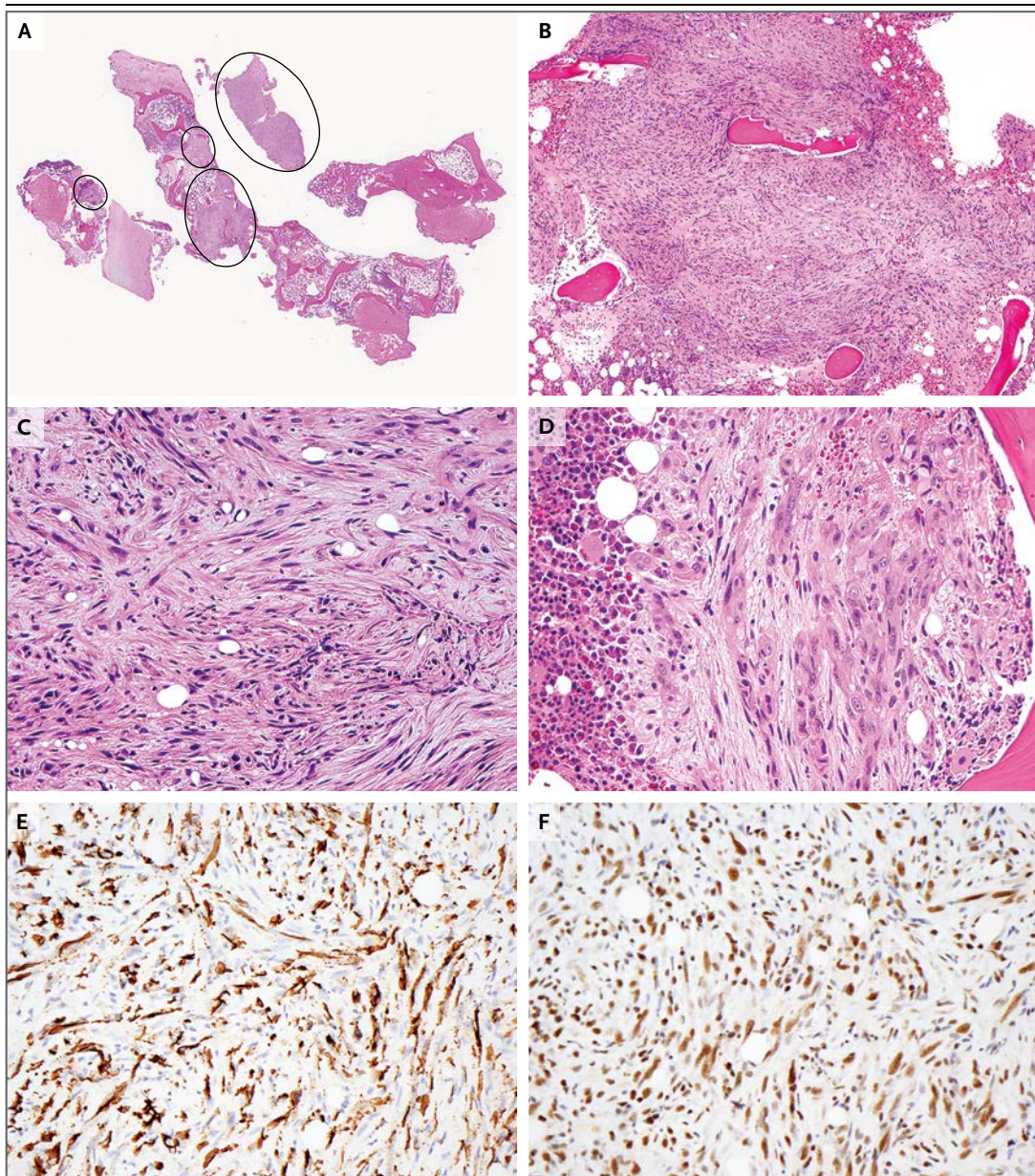
*Dr. Darcy A. Kerr:* Two bone marrow specimens from each iliac crest were obtained. A densely cellular neoplastic process was evident bilaterally, with infiltrating tumor cells surrounding pre-existing trabecular bone (Fig. 4A and 4B). Some regions of the tumor had a distinctly spindle-shaped appearance (Fig. 4C), and other areas had both spindled and epithelioid features. The epithelioid tumor cells formed cohesive, short cords (Fig. 4D). Both the spindle-cell and the epithelioid-cell components had moderate nuclear pleomorphism. The tumor stroma was largely fibrotic, but focal areas of pale-blue myxohyaline matrix were seen.

Immunohistochemical staining showed that the tumor cells were positive for the vascular endothelial markers CD31 (Fig. 4E) and FLI1 (Fig. 4F), as well as for D2-40, a marker of lymphatic endothelium. Staining for CD117 highlighted scattered mast cells.

Taken together, these findings point to an epithelioid spindle-cell tumor with endothelial differentiation. The spectrum of epithelioid vascular tumors is broad, with substantial morphologic overlap among entities. On the benign end of the spectrum is epithelioid hemangioma, which has a lobular growth pattern, causes distinct capillary-sized lumina, and is not associated with marked nuclear pleomorphism. On the malignant end of the spectrum is epithelioid angiosarcoma, which is characterized by the presence of solid sheets of hyperchromatic, frankly malignant-appearing epithelioid endothelial cells with prominent mitotic activity. Between these two entities on the spectrum is epithelioid hemangioendothelioma, a rare vascular tumor of low-to-intermediate-grade malignancy that is characterized by a myxohyaline or chondroid matrix. Epithelioid hemangioendothelioma tumor cells more frequently form cords and have more atypia than do the cells associated with epithelioid hemangioma; the tumor cells are not as pleomorphic as the cells associated with epithelioid angiosarcoma.<sup>8,9</sup>

The overall histologic features of this case supported a diagnosis of epithelioid hemangioendothelioma, although the patient had only a small amount of the characteristic matrix. Genetic studies have shown that 60 to 100% of patients with epithelioid hemangioendothelioma have a t(1;3) translocation.<sup>10-13</sup> Thus far, this translocation appears to be unique to and specific for epithelioid hemangioendothelioma. Candidate genes *WWTR1* and *CAMTA1*, transcriptional activators previously implicated in oncogenesis, were identified as a corresponding novel gene fusion, *WWTR1-CAMTA1*.<sup>11,12</sup> The role of the t(1;3)(p36.23;q25.1) translocation and its associated genes is just beginning to be defined. *CAMTA1* on 1p36.23 belongs to a family of calmodulin-binding transcription activators and is a well-known tumor-suppressor gene lost in a subset of neuroblastomas and gliomas. *WWTR1* (also called *TAZ*) on 3q25.1 is a transcriptional coactivator that is a downstream effector in the Hippo signaling pathway. This pathway has a role in controlling organ size by modulating cell proliferation and apopto-





**Figure 4. Bone Marrow—Biopsy Specimens from the Iliac Crest.**

Histologic examination of bone marrow specimens (Panels A through D, hematoxylin and eosin) reveals the presence of an infiltrative neoplasm of spindle and epithelioid cells occupying up to one third of the intertrabecular space (Panel A, outlined). There is infiltration of preexisting trabecular bone by spindled cells that are arranged in a vaguely fascicular pattern (Panel B), with prominent resorption lacunae in the bone that are indicative of osteoclastic activity and correlate with the lytic nature of the lesions that have been seen on imaging. The spindle-cell component (Panel C) shows hyperchromatic, ovoid or slightly tapered nuclei and a moderate amount of eosinophilic cytoplasm. Most of the tumor stroma is fibrotic in nature, but focal areas of pale-blue myxohyaline matrix are noted. The epithelioid component shows cohesive, short cords of tumor cells adjacent to unremarkable hematopoietic marrow (Panel D). The epithelioid tumor cells are characterized by round or slightly irregular nuclei with dispersed chromatin, occasionally prominent central nucleoli, and intermediate-grade nuclear atypia. Staining for CD31 is positive in a cytoplasmic distribution (Panel E, immunoperoxidase), and staining for FLI1 is positive in a nuclear distribution (Panel F, immunoperoxidase); these findings confirm vascular endothelial differentiation. A number of other stains (including stains for cytokeratin AE1–AE3–CAM5.2, CD34, factor VIIIa, human herpesvirus 8, S-100, CD1a, CD21, CD30, CD3, CD20, ALK-1, CD163, CD138, kappa, and lambda) were negative.

sis and is overexpressed in a number of cancers and cell lines in humans. The novel *WWTR1-CAMTA1* gene fusion presently appears to be unique to epithelioid hemangioendothelioma and could plausibly underlie its pathogenesis.

In this patient, FISH analysis of paraffin-embedded tumor sections for the t(1;3) translocation was negative. The overall constellation of findings is nonetheless consistent with epithelioid hemangioendothelioma. Although epithelioid hemangioendothelioma was originally described as a tumor arising in the vascular tissues of the arms and legs,<sup>8</sup> it has since been described in the liver, lungs, and bone; it can affect essentially any site in the body. It is possible for the bones to be the only site of disease involvement; more than half of all patients with epithelioid hemangioendothelioma have multifocal skeletal disease. Alternatively, bone involvement may be one component of a multiorgan disease.<sup>9</sup>

## DISCUSSION OF MANAGEMENT

### MANAGEMENT OF EPITHELIOID HEMANGIOENDOTHELIOMA

*Dr. Edwin Choy:* Epithelioid hemangioendothelioma is a rare malignant tumor that affects fewer than 300 patients per year in the United States and accounts for approximately 1% of all vascular neoplasms.<sup>8,9</sup> Clinically, it is treated as a low-to-intermediate-grade angiosarcoma because, as compared with high-grade angiosarcomas, metastasis is less likely to develop, disease progression or time to relapse is slower, and survival is longer, even in cases of advanced disease. Unfortunately, this patient presented with widespread disease at the time of the diagnosis.

When trying to decide on a treatment regimen for epithelioid hemangioendothelioma, we considered the patient's performance status, confounding illnesses, and sites of disease. Because the patient had radiologic evidence of multiple vertebral compression fractures, the initial treatment plan, even before a definitive diagnosis was made, included administration of narcotics, bisphosphonate therapy, and vertebral kyphoplasty for the purpose of supportive care. Epithelioid hemangioendothelioma is rare, and thus our choice of systemic therapy could not be guided by randomized clinical trials; instead, it was based on a review of all cases and small clinical trials described in the literature to identify agents with at least some evidence of biologic activity.

Because epithelioid hemangioendothelioma is a neoplasm of vascular origin, therapies that target angiogenesis in this disease were thought to be promising. Epithelioid hemangioendothelioma is known to express a wide variety of ligands and receptors for vascular endothelial growth factor (VEGF) isoforms.<sup>14</sup> Several published case reports have shown a clinical benefit of the VEGF inhibitor bevacizumab.<sup>15-18</sup>

A phase 2 study of bevacizumab therapy showed that two of seven patients with metastatic epithelioid hemangioendothelioma had a measurable decrease in tumor size.<sup>19</sup> Other antiangiogenic agents have also been reported to show evidence of activity when they are administered as single agents. These agents include sunitinib,<sup>20</sup> thalidomide,<sup>21-23</sup> lenalidomide,<sup>24</sup> and interferon- $\alpha$ .<sup>25-27</sup>

In addition to antiangiogenic therapy, standard chemotherapy has been reported to show evidence of activity. Such chemotherapeutic agents include gemcitabine,<sup>28</sup> carboplatin-etoposide,<sup>29</sup> and liposomal doxorubicin.<sup>30,31</sup> Although taxanes are active in the treatment of angiosarcoma, they have not yet shown activity in the treatment of epithelioid hemangioendothelioma.

After the diagnostic bone marrow biopsies were performed, this patient had severe pain that made the initiation of systemic therapy impossible. Therefore, specialists in radiation oncology were consulted for consideration of administration of radiation therapy to the most symptomatic sites of disease involvement.

### MANAGEMENT OF PAINFUL BONE METASTASES

*Dr. Kevin S. Oh:* In the management of painful spine metastases, the most important initial step is correctly identifying the cause of pain. Common causes of back pain that is associated with bone metastases are mechanical instability, tumor-related inflammation, nerve-root involvement, or a combination of these causes. Before initiating therapy for pain relief, cord compression requiring urgent surgical intervention must be ruled out.

Mechanical instability is typically due to vertebral-body fracture and is often position dependent, acute in onset, and unresponsive to glucocorticoids. In this patient, the acute onset of back pain after a sneeze points toward a mechanical cause. CT and MRI confirmed the collapse of T7 (Fig. 1 and 2). There are several treatment options to restore stabilization. In this case, percutaneous augmentation was an appropriate initial



strategy. Augmentation, such as vertebroplasty and kyphoplasty, is minimally invasive and involves the percutaneous injection of acrylic cement (such as methyl methacrylate) with the use of imaging guidance. Randomized trials of augmentation involving patients with osteoporotic fractures have not shown any benefit.<sup>32</sup> However, in selected cases of cancer-related fractures, augmentation has been associated with rapid and clinically significant pain relief.<sup>33,34</sup> Contraindications to augmentation include severe compression or instability, a large degree of epidural disease, and breach of the posterior vertebral-body cortex. In such cases, resection limited to gross disease or en bloc resection with surgical stabilization may be more appropriate.

Pain that results from tumor-related inflammation (so-called biologic pain) is often unremitting, subacute or chronic in onset, and responsive to glucocorticoids. When this patient's pain recurred after percutaneous augmentation, it was presumed that there was a biologic component, and cancer-directed therapy was thought to be required for pain relief. Systemic therapy may offer pain relief in particularly responsive types of cancer. Radiation therapy is a common palliative strategy that offers partial pain relief in 50 to 80% of patients with tumor-related inflammation and complete pain relief in 20 to 40% of patients. Pain relief often does not occur until several weeks after completion of radiation therapy. The likelihood and degree of pain relief depends on the histologic type of cancer.<sup>35</sup>

There is wide variation in the dose and fractionation of radiation used for palliation of painful bone metastases. Multiple randomized trials that have compared a single fraction of radiation therapy at 8 Gy with regimens consisting of multiple fractions for the treatment of uncomplicated bone metastases have shown no significant differences among these regimens in achieving pain relief.<sup>36-38</sup> A single fraction at 8 Gy has the advantage of patient convenience and cost-effectiveness<sup>35</sup> but is associated with higher rates of retreatment,<sup>39</sup> perhaps because of increased willingness among clinicians to offer repeat irradiation after only a single fraction of 8 Gy. The technology used to deliver radiation for bone metastases can be radiograph-based and two-dimensional or CT-based and three-dimensional, depending on the degree of clinical complexity.

Palliative irradiation was administered in this

patient at 30 Gy in 10 fractions to T6–T8 and at 35 Gy in 14 fractions to the right hip, with the use of CT-based three-dimensional treatment planning. He had considerable relief from pain, and his need for pain medication decreased.

*Dr. Choy:* This patient was started on bevacizumab while he completed his course of palliative irradiation to the spine. Once radiation therapy was completed, he received combination chemotherapy with carboplatin, paclitaxel, and bevacizumab — a commonly used regimen for metastatic non-small-cell lung cancer.<sup>40</sup> He initially had a brief period of clinical improvement after the administration of chemotherapy had begun. His need for narcotics decreased, and his mobility increased. He was able to perform activities of daily living and enjoy time with his family.

*Dr. Huang:* Follow-up MRI of the lumbar spine that was performed 2 months after initial diagnosis revealed an increase in the size and number of the lesions throughout the lumbar spine, including a new pathologic compression fracture of L1 (Fig. 2B).

*Dr. Choy:* Unfortunately, because follow-up imaging revealed progression of disease and the development of multiple pathologic fractures, including fractures involving the right acetabulum and lumbar spine, the patient required hospitalization for pain control and additional palliative radiation therapy. Shortly after discharge, he was rehospitalized for shortness of breath and hemoptysis. Chest imaging indicated severe pneumonitis. Although he initially improved with a high dose of glucocorticoids, fulminant *Clostridium difficile* colitis developed, and the patient died after a brief course of ventilatory support.

*Dr. Nancy Lee Harris (Pathology):* What do you think was the primary site of this tumor?

*Dr. Choy:* The tumor most likely arose within the vasculature of the bone; either the spine or the rib lesions were potentially large enough to be considered the primary tumors, with metastases to other sites in the bone.

*Dr. Harris:* Do epithelioid hemangioendothelioma tumors typically metastasize in the tissue of origin? It is quite striking that this tumor involves only the bone despite being so widespread in the bone.

*Dr. Choy:* I think localization of the tumor in the bone is peculiar to this case. In most such cases, tumors metastasize to the lungs. But this tumor showed bone-seeking behavior, which is

an aspect of this patient's tumor biology that we don't fully understand.

**Dr. Bruce A. Chabner** (Medical Oncology): It is frustrating that sarcomas lack clear driver mutations, such as the *BRAF* or *EGFR* mutations that are seen in epithelial tumors, which can be targets of therapy. What is needed to understand the biology of sarcomas and to develop targeted treatments?

**Dr. Choy:** About one third of soft-tissue sarcomas and some bone sarcomas are defined by particular chromosomal translocations, suggesting that the resulting fusion protein could be a therapeutic target. For epithelioid hemangioendothelioma, the translocation involving chromosomes 1 and 3 does give us a hint about the biology of the tumor and could inform therapeutic strategies. Although we do not understand how to inhibit transcription factors yet, a number of research groups are working on this problem.

**Dr. Harris:** Given the aggressive clinical course of the disease, why is this not a case of epithelioid angiosarcoma?

**Dr. Kerr:** On the spectrum of epithelioid vascular tumors, this tumor would perhaps fall somewhere between epithelioid hemangioendothelioma and epithelioid angiosarcoma. Epithelioid angio-

sarcoma certainly is the leading differential diagnosis histologically. We thought that the tumor-cell cytomorphologic features were not overtly malignant-appearing enough to warrant a diagnosis of epithelioid angiosarcoma and that the overall histologic pattern was more consistent with epithelioid hemangioendothelioma. Most epithelioid hemangioendotheliomas follow an indolent clinical course, but it is estimated that approximately 15% of patients with epithelioid hemangioendothelioma die of the disease, so the aggressive nature of this patient's clinical course alone does not necessitate the designation of angiosarcoma.<sup>9,13</sup>

## ANATOMICAL DIAGNOSIS

### Epithelioid hemangioendothelioma.

This case was presented at the Cancer Center Grand Rounds.

Dr. Choy reports receiving consulting fees from Amgen, Pfizer, Bayer, and NPS Pharmaceuticals; and Dr. Attar, receiving consulting fees from Celgene and Janssen Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://NEJM.org).

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